PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32467A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/04152	International filing date *(day/month/year)* 22.04.2003	Priority date *(day/month/year)* 23.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/196		
Applicant NOVARTIS AG ET AL.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.10.2003	18.05.2004
Name and mailing address of the International preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Beranová, P Telephone No. +49 30 25901-333

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/04152

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-17 as originally filed

Claims, Numbers

1-9 filed with telefax on 20.01.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 5 - 9

   because:

   ☒ the said international application, or the said claims Nos. 1, 5 - 7 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 8, 9

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1 - 7 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1 - 7
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1 - 7
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	2 - 4
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3.1 Claims 1 and 5 - 7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Non-unity

4.1 The Examining Division agrees with the objection put forward by the Search Division as to lack of unity (Rule 13 PCT), the reasons for the objection being as already indicated in the Search Report.

4.2 In response to the invitation to restrict or pay additional search fees, the applicant has neither restricted nor paid additional fees. As a consequence, only the searched subject-matter is subject of the international preliminary examination, i.e. claims 1 - 7.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 In light of the documents cited in the international search report, the invention as claimed appears to meet the criteria mentioned in Article 33(1) PCT, i.e. it appears to be novel and to involve an inventive step.

5.2 For the assessment of the present claims 1 and 5 - 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

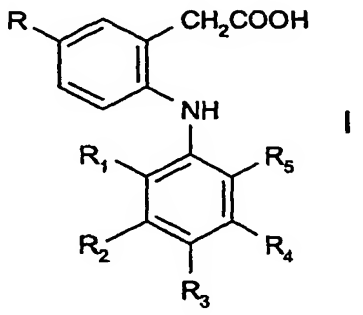
Re Item VI
Additional observations

6.1 The term "prodrug ester" used in claims 1 - 4 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

6.2 The embodiments of the invention described on page 1, 5th paragraph ("rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib") do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

CLAIMS

1. A method of treating cancer pain in a subject in need of such treatment which comprises administering to the subject an effective amount of a COX-2 inhibitor of formula I



I

wherein:

R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

a pharmaceutically acceptable salts thereof; or

a pharmaceutically acceptable prodrug esters thereof.

2. Use of a compound of formula I as defined in claim 1 (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament for treatment of cancer pain.

3. Use of a compound of formula I as defined in claim 1 (or pharmaceutically acceptable salt or prodrug ester thereof) for the treatment of cancer pain.

4. A package comprising a compound of formula I as defined in claim 1 (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for use in the treatment of cancer pain.

5. A method according to claim 1 or use according to claim 2, in which the compound of formula I is 5-methyl-2-(2-chloro-6-fluoroanilino)-phenylacetic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof.

6. A method according to claim 1 or use according to claim 2, for the treatment of bone cancer pain.

7. A method according to claim 1 or use according to claim 2, in which the compound of formula I is in the form of an oral composition or an injectable composition.

8. A method for the inhibition of bone loss, advantageously in cancer, which comprises administering an effective amount of a COX-2 inhibitor of formula I (or an ester or prodrug thereof) as defined in claim 1 to a subject in need of such treatment.

9. Use of a COX-2 inhibitor of formula I (or an ester or prodrug thereof) as defined in claim 1, for the preparation of a medicament for the inhibition of bone loss, in particular bone loss in cancer.